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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,967	02/02/2001	Andrei P. Guzaev	ISIS-4682	9641

32650 7590 05/27/2004

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 05/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,967	GUZAEV ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11-15,21,36-40,47-52,56-60,66,81-85,92-101,103 and 104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the species wherein D^+ is protonated aromatic heterocyclic amine and E^- is tetrazolide anion in Paper No. 6 dated December 24, 2002 is acknowledged. The restriction requirement was made FINAL in Paper No. 11 dated June 11, 2003.

Applicant's Response dated February 25, 2004

2. In the Response filed February 25, 2004, claim 48 was amended.

3. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104 are pending. An action on the merits of claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104 is contained herein below.

4. The rejection of claims 48-52, 56-60, 66, 81-85, 92-95, and 104 under 35 U.S.C. 112, second paragraph, has been rendered moot in view of applicant's response dated February 25, 2004.

5. The rejection of claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-97, and 104 under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. Proceedings of the 2nd International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (Caruthers) in combination with Nurminen et al. *J. Chem. Soc., Perkin Trans. 2* (1999), pages 2551-2556 (Nurminen) is maintained for the reasons of record set forth in the Office Action dated December 2, 2003.

6. The rejection of claims 98-101 and 103 under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. Proceedings of the 2nd International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (Caruthers) in combination with Nurminen et al. *J. Chem. Soc., Perkin Trans. 2* (1999), pages 2551-2556 (Nurminen) is maintained for the reasons of record set forth in the Office Action dated December 2, 2003.

Objections/Rejections of Record Set Forth in Office Action

Dated December 2, 2003

7. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-97, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. Proceedings of the 2nd International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (Caruthers) in combination with Nurminen et al. *J. Chem. Soc., Perkin Trans. 2* (1999), pages 2551-2556 (Nurminen).

Claims 1-6, 11-15, 21, 36-40, and 47 are drawn to a method comprising reacting a nucleoside phophoramidite with a support bound oligomer in the presence of a neutralizing agent, wherein said neutralizing agent is an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D^+E^-. Claims 48-52, 56-60, 66, 81-85, 92-95, and 104 are drawn to a method of forming an internucleoside linkage in the presence of a neutralizing agent, wherein said neutralizing agent is an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine a guanidine, or a salt of formula D^+E^-.

Claims 96-97 are drawn to a method comprising the steps of: a) providing a solid support having a 5'-O-protected phosphorous-linked oligomer bound thereto; b) deprotecting the 5'-hydroxyl of the protected oligomer; c) optionally washing the deprotected phosphorous-linked oligomer on the solid support; d) contacting the support bound oligomer with a solution comprising a 5'-protected nucleoside phosphoramidite and a neutralizing agent; and e) oxidizing or sulfurizing the phosphite triester linkage.

Caruthers teaches the synthesis of oligonucleotides using the phosphoramidite method corresponding to the instantly claimed method. Using the procedure outlined in Table 1 (page 6), RNA was synthesized manually. Support bound nucleoside (**3a-d**) was first converted to **5a-d** by treatment with 0.3% DCA to remove the dimethoxytrityl group. After washing with dichlormethane and acetonitrile, the appropriate nucleoside phosphoramidite (**4a**, **4b**, **4c**, or **4d**) and tetrazole were added to the support. Condensations were allowed to proceed for 15 minutes. Following an aqueous, hydrolytic wash the final two steps oxidation with I_2 and capping with benzoic anhydride.

Caruthers differs from the instantly claimed invention in that Caruthers does not teach the use of a neutralizing agent of D^+E^-; however, the use of a neutralizing agent of the formula D^+E^- as a suitable replacement for tetrazole would have been obvious to one of ordinary skill in the art when the teachings of Nurminen are considered.

Nurminen teaches that ammonium azolide salts were found to be considerably more efficient catalysts than the corresponding azole acids or tertiary amine bases (Abstract, Fig. 2, Fig. 3). For instance, the relative rates obtained with *N,N-diisopropylethylammonium tetrazolide, N,N*-diisopropylethylamine and tetrazole were

104, 28 and 1, respectively. The salts of strong protolytes are better catalyst than those of weak ones. Other suitable tetrazole and ammonium tetrazolide salts are shown in Table 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to replace tetrazole with an ammonium azolide salt in the process taught by Caruthers as Nurminen expresses provides motivation for doing so [ammonim azolide salts were found to be considerably more efficient catalysts than the corresponding azole]. The examiner finds one of ordinary skill in the art as being a PhD in the field of nucleoside/nucleotide synthesis. Based on the teaching of Nurminen, the skilled artisan would have a reasonable expectation of success in substituting tetrazole with an ammonium azolide salt for form internucleoside linkages. The selection of a known material based on its suitability for its intended use is well within the purview of one of ordinary skill in the art at the time of the invention and is *prima facie* obvious.

8. Applicant's arguments filed February 25, 2004 have been fully considered but they are not persuasive. Applicant argues that the instantly claimed processes differ from that of the cited art because the Nurminen reference shows the use of certain neutralizing agents in the context of reacting diisopropylphosphonite with t-butyl alcohol as opposed to in the context of oligomer synthesis. Applicant further argues that even if one were to combine the teachings, one would not arrive at any instantly claimed invention.

While the examiner agrees that Nurminen does not show the use of the neutralizing agents in oligomer synthesis, applicant is reminded that no anticipatory

rejections have been set forth on the record. However, Nurminen clearly suggests the use of the neutralizing agents for the use in DNA synthesis as set forth in the opening paragraph. One of ordinary skill in the art would indeed expect the neutralizing agents shown in Table 1 to be effective catalysts in DNA synthesis.

9. Claims 98-101 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. Proceedings of the 2nd International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (Caruthers) in combination with Nurminen et al. *J. Chem. Soc., Perkin Trans. 2* (1999), pages 2551-2556 (Nurminen).

Claims 98-101 and 103 are drawn to a composition comprising a 5'protected nucleoside phosphoramidite, a salt of formula D^+E^-, and a solid support.

Caruthers teaches support bound nucleoside (**3a-d**) which are first converted to **5a-d** by treatment with 0.3% DCA to remove the dimethoxytrityl group. After washing with dichlormethane and acetonitrile, the appropriate nucleoside phosphoramidite (**4a**, **4b**, **4c**, or **4d**) and tetrazole [neutralizing agent] were added to the support.

Caruthers differs from the instantly claimed invention in that Caruthers does not teach the use of a neutralizing agent of formula D^+E^-; however, the use of a neutralizing agent of the formula D^+E^- as a suitable replacement for tetrazole would have been obvious to one of ordinary skill in the art when the teachings of Nurminen are considered.

Nurminen teaches that ammonium azolide salts were found to be considerably more efficient catalysts than the corresponding azole acids or tertiary amine bases

(Abstract, Fig. 2, Fig. 3). For instance, the relative rates obtained with *N,N-diisopropylethylammonium tetrazolide, N,N*-diisopropylethylamine and tetrazole were 104, 28 and 1, respectively. The salts of strong protolytes are better catalyst than those of weak ones. Other suitable tetrazole and ammonium tetrazolide salts are shown in Table 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to replace tetrazole with an ammonium azolide salt in the composition taught by Caruthers as Nurminen expresses provides motivation for doing so [ammonim azolide salts were found to be considerably more efficient catalysts than the corresponding azole]. The examiner finds one of ordinary skill in the art as being a PhD in the field of nucleoside/nucleotide synthesis. Based on the teaching of Nurminen, the skilled artisan would have a reasonable expectation of success in substituting tetrazole with an ammonium azolide salt for form internucleoside linkages. The selection of a known material based on its suitability for its intended use is well within the purview of one of ordinary skill in the art at the time of the invention and is *prima facie* obvious.

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While the examiner agrees that Nurminen does not show the use of the neutralizing agents in oligomer synthesis, applicant is reminded that no anticipatory rejections have been set forth on the record. However, Nurminen clearly suggests the use of the neutralizing agents for the use in DNA synthesis as set forth in the opening paragraph. One of ordinary skill in the art would indeed expect the neutralizing agents shown in Table 1 to be effective catalysts in DNA synthesis.

Conclusion

11. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104 are pending. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-97, and 104 are rejected. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on M-F 10:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

Dr. Samuel Barts
Primary Patent Examiner
Technology Center 1600

ptl
May 24, 2004